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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	07/110,791	KING ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60,61,68 and 69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60,61,68 and 69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 October 1987* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. The Notice of Abandonment mailed March 21, 2006, is vacated in view of the fact that claims 60 and 61 were indicated to be patentable in the Interference Initial Memorandum mailed September 18, 1996.

2. The amendment filed May 3, 2006, is acknowledged and has been entered. Claims 44, 46, and 47 have been canceled. Claims 68 and 69 have been added.

3. Claims 60, 61, 68, and 69 are presently pending in the application.

4. Claims 60, 61, 68, and 69 are currently subject to examination.

Allowable Subject Matter

5. The indicated allowability of claims 50 and 61 is withdrawn in view of the grounds of rejection that follow.

Numbering of the Claims

6. It appears that claims numbered 16 and 17 were never added; thus, claims 18-69 are currently misnumbered. Nonetheless, given the fact that this error was not previously discovered during the lengthy period of prosecution that followed, any immediate requirement to number claims consecutively is waived; however, Applicant is advised to remedy this deficiency in replying to this Office action by submitting a set of claims in which the claims are properly numbered in consecutive order.

Priority

7. Applicant's claim under 35 U.S.C. §§ 119(e) and/or 120, 121, or 365(c) for benefit of the earlier filing date of Application No. 06/836,414, filed March 5, 1986, is acknowledged.

However, claims 60, 61, 68, and 69 do not properly benefit under §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). See M.P.E.P. § 201.11.

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely October 21, 1987.

Drawings

8. The drawings set forth as Figures 1 and 3 are objected to because the figures depict nucleotide and/or amino acid sequences, which are not identified by sequence identification numbers, either in the figure or in the brief description of figures beginning at page 5 of the specification, as originally filed. Sequences appearing in the specification and/or drawings must be identified by a sequence identifier in accordance with 37 C.F.R. 1.821(d); sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

A replacement drawing sheet, including the correction, is required, if the drawings are objected to. See 37 CFR 1.121(d). However, this ground of objection would be withdrawn, so that a replacement drawing would be not be required, if

Applicant were to amend the brief description of the figures beginning at page 5 of the specification to include sequence identification numbers.

Specification

9. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of such improperly demarcated trademarks appearing in the specification include Speedvac™ (see, e.g., page 16, line 19, of the specification, as originally filed) and Packagene™ (see, e.g., page 17, line 13).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

10. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the sequences depicted in Figures 1 and 3 are not identified by sequence identification numbers, either in the figure or in the brief description of figures beginning at page 5 of the specification, as originally filed.

In addition, there are also sequences set forth in the specification at page 8, beginning in line 13, page 26, beginning in line 16, and page 28, beginning in line 7, which are not identified by sequence identification numbers.

Applicant must provide appropriate amendments to the specification or drawings inserting the required sequence identifiers. Sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with an amendment directing its entry into the specification and a statement that the content of both copies are the same and, where applicable, include no new matter.

11. The specification is objected to because the pages are not numbered consecutively in accordance with the requirements set forth under 37 C.F.R. § 1.152[1], which states: "Other than in a reissue application or reexamination proceeding, the pages of the specification including claims and abstract must be numbered consecutively, starting with 1, the numbers being centrally located above or preferably below, the text." M.P.E.P. § 608.01.

Appropriate correction is required.

12. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

[1] As an example of this deficiency, the 10th page of the specification is improperly numbered "9a".

Claims 60, 61, and 68 are directed to a process of diagnosing or classifying cancers in patients by detecting abnormal expression of a protein, which is encoded by a MAC117 gene, in "a body sample" acquired from the patient using an immunoassay.

As evidenced by the declaration of Matthias H. Kraus under 37 C.F.R. § 1.132 filed June 17, 1996, the term "body sample" is not used solely to refer to a sample of tissue or tumor, since the body sample may instead be a sample of serum or effusion, or perhaps any other sample that might be acquired from the body of a patient, other than tissue or tumor cells.

In contrast to the evident breadth of the term "body sample", as it is used in the context of the language of the claims, the descriptive portion of this application appears to describe only samples of tissue or tumor; the disclosure does not describe the use of samples of sera, effusions, or any other bodily component that might be acquired from the body of a patient, other than tissue or tumor cells.

M.P.E.P. § 608.01(o) states:

> While an applicant is not limited to the nomenclature used in the application as filed, he or she should make appropriate amendment of the specification whenever this nomenclature is departed from by amendment of the claims so as to have clear support or antecedent basis in the specification for the new terms appearing in the claims. This is necessary in order to insure certainty in construing the claims in the light of the specification, *Ex parte Kotler,* 1901 C.D. 62, 95 O.G. 2684 (Comm'r Pat. 1901). See 37 CFR 1.75, MPEP § 608.01(i) and § 1302.01.

M.P.E.P. § 608.01(o) further states that if the examiner determines that the claims presented late in prosecution do not comply with 37 CFR 1.75(d)(1), applicant will be required to make appropriate amendment to the description to provide clear support or antecedent basis for the terms appearing in the claims provided no new matter is introduced.

It is submitted that it would not be clear from a reading of the descriptive portion of this application, alone, where there is support for the language of the claims because apart from describing tissue samples and tumor cells, the disclosure fails to describe the "body samples" to which the claims are directed.

Claim Objections

13. Claims 61 and 68 are objected to because claims recite, "the 423 nucleotides set forth in Figure 1 or the restriction pattern set forth in Figure 5A".

M.P.E.P. § 2173.05(s) states:

> "Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted).

Thus, claims must, under modern claim practice, stand alone to define invention, and incorporation into claims by express reference to specification and/or drawings is not permitted except in very limited circumstances.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

14. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

15. Claim 69 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The considerations that are made in determining whether a claimed invention is supported by either a specific and substantial asserted utility or a well-established utility are outlined by the published Utility Examination Guidelines (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: http://www.gpoaccess.gov/.

Briefly, a "specific and substantial" asserted utility is an asserted, expressly identified utility that is specific to the particular nature and substance of the claimed subject matter, and which would be immediately available for application in a "real-world" context by virtue of the existing information disclosed in the specification and/or on the basis of knowledge imparted by the prior art, such that its use would not require

or constitute carrying out further research to identify or reasonably confirm its usefulness in this context. A "well-established" utility is a credible, specific, and substantial utility, which is well known, immediately apparent, and implied by the specification, and based on the disclosure of the properties of a material or subject matter, either alone or taken with the knowledge of one skilled in the art.

Claim 69 is drawn to a method of detecting a gene.

The claim recites no intended use or purpose, however, apart from the detection of a gene.

What specific and substantial utility or well established utility might such an invention have?

In light of the disclosure, it appears that the claimed invention is not a useful process in and of itself, but rather a mere part of other disclosed processes that have asserted utilities.

For example, claim 60 is directed to a process of diagnosing human cancer in a patient by detecting amplification of a MAC117 gene; and though it is very likely the detection of amplification of the gene necessarily involves the detection of the gene, it is not the presence of the gene alone that provides an indication that the gene is amplified. This is because the gene is expectedly present in every cell of the human body, though perhaps amplified in only a fraction of those cells. So, in order to detect amplification of the gene, the practitioner must not only detect the gene, but must quantify the gene.

As such, it is not apparent that the specification asserts that the claimed invention itself has any specific and substantial utility; and it is not evident that it has any well established utility either.

If the invention is actually only intended for use as an active step of some other process, rather than a useful process, in and of itself, having any one particular objective or purpose, the claim fails to meet the utility requirement set forth under 35 U.S.C. § 101.

If not just a mere part of different useful inventions disclosed in this application, perhaps the claimed invention might be useful as an investigative tool, but Applicant is

reminded that such an invention lacks the requisite specific and substantial utility of a patentable invention under 35 U.S.C. § 101.

For example, the claimed invention might be used to make a determination that a cell contains a MAC117 gene that is detected using the invention, but because this would hold true of any process of detecting any gene, such utility is not a specific utility; and moreover, any benefit that might be derived by the public for a grant of a patent monopoly of the claimed process of detecting the disclosed gene is not specific to the nature of the process, or even to the substance and nature of the gene.

Furthermore, based upon the information contained in the application, it would seem that there is no reason for detecting the presence of a MAC117 gene, apart from facilitating the objectives and aims of basic research directed toward the study of the function of the gene.

In other words, given only the benefit of the existing disclosure of the invention, it is submitted that the claimed invention, in and of itself, cannot be regarded as having any immediate, practical, and beneficial utility.

Notably, the idea of detecting a given gene by hybridizing a nucleic acid probe that anneals to the gene is not a novel concept; such processes have been practiced to detect genes since their original conception years ago[2].

Furthermore, the gene to which the claim is directed is not novel, since the prior art teaches a gene encoding a polypeptide having the molecular weight of about 185 kDa, which is expressed, for example, by breast cancer cells[3]; so the idea of detecting a “MAC117 gene” is also not an original concept.

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[2] See, e.g., Southern (*J. Mol. Biol.* 1975 Nov 5; **98** (3): 503-517), which may have first described such a process; and then, as an example of such general applicability of such processes, see Bergmann et al. (*J. Virol.* 1980 Sep;**35** (3): 968-971), which describes a determination of the sites of integration of the avian myeloblastosis-associated virus type 2 DNA by Southern blot analysis of cellular DNA from infected chicken embryonic fibroblasts; see entire document (e.g., the abstract).

[3] See, e.g., Coussens et al. (*Science*. 1985 Dec 6; **230**: 1132-1139), which describes a "MAC117 gene" designated "HER2", as well as a process of detecting the gene by Southern blot hybridization (see entire document; e.g., page 1133, Figure 1; and page 1137, Figure 5).

Though the invention might be used as a basic research tool, only further investigation can determine if or how the claimed process itself can be used in a specific manner that might immediately benefit the public by its practice.

Accordingly, here, it would seem that the claims amount to no more than a mere invitation to the artisan to elaborate a "real-world" use for the claimed process of detecting a MAC117 gene, or alternatively to develop useful other processes comprising, as an integral active step, the detection of a MAC117 gene.

Summarizing these points, inasmuch as the claimed invention has no requisite objective or purpose, apart from the detection of a gene, it would seem that the invention, in and of itself, has no specific and substantial utility.

The U.S. Supreme Court addressed the issue of utility under 35 U.S.C. § 101 in deciding *Brenner, Comr. Pats. v. Manson,* 148 U.S.P.Q. 689 (US SupCt, 1966). The Court expressed the opinion that all chemical compounds are "useful" to the chemical arts *when this term is given its broadest interpretation*; nonetheless, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The Court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. Id., at 695.

Further, the Court opined,

> [W]e are [not] blind to the prospect that what now seems without "use" may tomorrow command the grateful attention of the public. But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. Id., at 696.

It is submitted the instant situation is directly analogous to that which was addressed by the Court in deciding *Brenner, Comr. Pats. v. Manson*, since here too it might be said that all processes by which a given gene is detected are "useful" in the biochemical arts when the term is given its broadest interpretation, but nevertheless § 101 requires that an invention have either an immediately obvious or fully disclosed

"real world" utility, which the claimed invention lacks because the specification does not disclose a currently available "real world" use for the claimed method of detecting a MAC117 gene.

To employ the disclosure of the claimed invention of detecting a MAC117 gene in any other useful process, apart from those disclosed in the specification, such as the claimed process of diagnosing cancer, would require further research, which should be regarded as constituting part of the inventive process. Because the specification does not disclose a currently available, "real world" use for the claimed invention, the requirements set forth under 35 U.S.C. § 101 have not been met.

To fulfill the requirements of § 101, the skilled artisan must be able to use a claimed invention in the manner asserted by Applicants' to provide some immediate benefit to the public. See *Nelson v. Bowler and Crossley*, 206 USPQ 881 (CCPA, 1980).

The existing information disclosed by Applicants' application would merely provide the artisan with an invitation to perform further investigations to discover how the claimed invention might be useful, either in and of itself, or as an integral part of some other useful process. Although such additional investigation might ultimately lead to a derivation of a specific benefit, an immediate benefit could not be derived from the use of the claimed invention because the existing information is insufficient to enable the artisan to use the claimed antibody-antigen binding reaction in a specific, substantial and credible manner to provide an immediate benefit. Although the disclosure of the claimed polynucleotide might tomorrow command the grateful attention of the public, the Court has decided:

> [A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

Brenner, Comr. Pats. v. Manson, 148 U.S.P.Q. 689 at 696 (US SupCt, 1966).

Claim Rejections - 35 USC § 112

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 60, 61, 68, and 69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 60, 61, 68, and 69 are indefinite for the following reasons:

(a) Claims 60, 61, 68, and 69 are indefinite because the claims use of the designation “MAC117 gene" as the sole means of identifying the genes and/or other nucleic acids to which the claims refer.

In general, the use of laboratory designations only to identify a particular gene or nucleic acid molecule renders claims indefinite because different laboratories may use the same laboratory designations to define completely distinct genes and other nucleic acid molecules.

Indeed, in this case, it appears that other terms, such as "HER-2", "Neu", "c-ErbB-2" have been used in the art to identify the same gene or genes to which the claims may be directed.

Furthermore, it is aptly noted that the same term is often used in the art to describe, not one gene or nucleic acid molecule, but rather a plurality of genes (e.g., alleles, polymorphic variants, etc.), which are structurally and/or functionally related, but otherwise distinct. For example, the same term is often used to describe allelic variants, which encode structurally and/or functionally disparate proteins (i.e., “isoforms”).

In addition, claims 60, 61, and 68 are directed to any of a plurality of “protein products” of the MCA117 gene, which may only be identified by the recited designation of the gene encoding those proteins. However, as explained, the use of laboratory designations only to identify a particular gene renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct genes and/or other nucleic acid molecules, which encode structurally and/or functionally disparate proteins. Though such structurally and/or functionally different

proteins are encoded by a single gene, they are the products resulting from translation of alternatively spliced transcripts of that gene.

In this case, there have been at least three isoforms described, which are encoded by a single "MAC117" gene, but are the translation products of differentially spliced transcripts; and it appears that each is expressed in different manners and extents by different types of cells, and that each may have substantially different specific activities and biologic functions.

Scott et al. (*Mol. Cell. Biol.* 1993 Apr; **13** (4): 2247-2257) describes an isoform, which although expected to be produced as a secreted variant of the cell membrane-bound "HER2 receptor", which contains only the extracellular ligand binding domain, is actually sequestered to within the cell; see entire document (e.g., the abstract).

Aigner et al. (*Oncogene*. 2001 Apr 19; **20** (17): 2101-2111) describes the expression of a similarly sized 100 kDa splice variant, which acts as an endogenous inhibitor of tumor cell proliferation; see entire document (e.g., the abstract).

Doherty et al. (*Proc. Natl. Acad. Sci. U S A.* 1999 Sep 14; **96** (19): 10869-10874) has described a variant having a molecule weight of only about 68 KDa, which is encoded by a mRNA molecule that is expressed at reduced levels relative to mRNA encoding the 185 KDa isoform, which is often overexpressed in certain carcinoma cells containing the amplified gene; see entire document (e.g., the abstract). Unlike the larger 100 KDa isoform described by Scott et al. (*supra*), Doherty et al. teaches this isoform is secreted by cells; see, e.g., the abstract.

This position is further supported, for example, by the recent disclosure of Koletsa et al. (*Neoplasia*. 2008 Jul; **10** (7): 687-696). Koletsa et al. again teaches the "MAC117 gene" encodes a plurality of protein variants, which are the products of alternatively spliced mRNA molecules; see entire document (e.g., the abstract; and the paragraph bridging pages 687 and 688). Koletsa et al. teaches the better characterized isoform is encoded by a transcript that retains intron 8, such that the protein has a unique carboxy-tail sequence (paragraph bridging pages 687 and 688). Koletsa et al. teaches this isoform is a soluble protein, because it lacks a transmembrane domain, and can be secreted from cells (page 688, column 1). As might be expected in light of

their different structures, Koletsa et al. teaches the soluble isoform appears to have functions that are very unlike those of other isoforms, which are displayed at the surfaces of cells and not secreted; see, e.g., page 688, column 1.

Then, as final example of the reasons that the use of such nomenclature alone is insufficient to particularly point out and distinctly claim the subject matter that is regarded as the invention, it is noted that the same terms are frequently used to identify gene and/or the polypeptides encoded by those genes that occur in different species of animals; although sharing certain structural and/or functional characteristics, these genes and their products often have markedly distinct structures and/or functions (e.g., orthologs and paralogs).

35 U.S.C. § 112, second paragraph, requires the claim define the metes and bounds of the subject matter that is regarded as the invention with such clarity and particularity to permit the skilled artisan to know or determine infringing subject matter; because the terms used to describe the polypeptides to which the claims are directed do not unambiguously identify those polypeptides, this requirement has not been met.

Accordingly, it is suggested that this issue might be remedied by amending the claims to include a recitation of the nucleotide sequence of the gene or other nucleic acid molecules to which the claims are directed, or alternatively the amino acid sequence of the polypeptides encoded by those genes, by reference to one or more specific sequence identification numbers of corresponding to the same nucleotide or amino acid sequences as set forth in the Sequence Listing. This is because the nucleotide sequence of a nucleic acid molecule and the amino acid sequence of a polypeptide are unique identifiers that unambiguously define a given nucleic acid molecule and polypeptide, respectively.

(b) Claims 60, 61, and 68 are indefinite because the claims are directed to a method comprising detecting "increased" expression of a gene in a tissue or tumor cell sample of a patient.

The term "increased" is a relative term; yet, it cannot be ascertained relative to what standard the expression of the gene must be compared in practicing the process

that is regarded as the invention, so as to determine if the level is increased in the tissue or tumor cell sample of the patient.

The metes and bounds of the subject matter that is encompassed by the claims will vary widely, depending upon which standard value is used in the comparison; and the value of the standard might also vary substantially depending upon how it is determined.

In accordance with a recent decision by the Federal Circuit (*Halliburton Energy Services Inc. v. M-I LLC*, 85 USPQ2d 1654, 1658 (Fed. Cir. 2008)):

> 35 U.S.C. § 112, ¶ 2 requires that the specification of a patent "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." Because claims delineate the patentee's right to exclude, the patent statute requires that the scope of the claims be sufficiently definite to inform the public of the bounds of the protected invention, i.e., what subject matter is covered by the exclusive rights of the patent. Otherwise, competitors cannot avoid infringement, defeating the public notice function of patent claims. Athletic Alternatives, Inc. v. Prince Mfg., Inc., 73 F.3d 1573, 1581 (Fed. Cir. 1996) ("[T]he primary purpose of the requirement is 'to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their [respective] rights.'") (quoting Gen. Elec. Co. v. Wabash Appliance Corp., 304 U.S. 364, 369, (1938)). The Supreme Court has stated that "[t]he statutory requirement of particularity and distinctness in claims is met only when [the claims] clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." United Carbon Co. v. Binney & Smith Co., 317 U.S. 228, 236 (1942).

The failure of the claims to make evident the value of the standard that must be applied, or the means by which that value is necessarily determined, render the claims indefinite; and moreover the metes and bounds of the subject matter that is regarded as the invention cannot be determined with the requisite clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

(c) Claims 60 and 68 are indefinite because claim 60 recites, "by hybridizing nucleic acid derived from a tissue or tumor cell sample of said patient with a nucleic acid probe of the MAC117 gene" and claim 68 recites, "by hybridizing nucleic acid derived from a tissue or tumor sample containing cells from a patient diagnosed with cancer with a nucleic acid probe of the MAC117 gene".

It cannot be ascertained which "nucleic acid" is necessarily hybridized with the probe, or how that "nucleic acid" is necessarily *derived* from a tissue or tumor cell sample of the patient.

Then, as explained in the rejections that follow, it is imperative that the type and nature of the "nucleic acid" be known in order to practice the claimed process in a manner that might achieve the intended result.

Though the specification describes certain assays as utilizing particular types of nucleic acids, which are isolated from cells or tissues, Applicant is reminded that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Thus, despite the disclosure, the claims cannot be unambiguously construed as encompassing any particular process that is described therein; and therefore the metes and bounds of the subject matter that is regarded as the invention cannot be determined with the requisite clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

(d) Claim 60 is indefinite because the claim recites the limitation, "the protein product of the MAC117 gene". Because it would appear that there are a plurality of gene products encoded by the "MAC117 gene", since, for example, the human gene encoding the 185 kDa isoform is the same gene that encodes the 100 kDa isoform, it cannot be determined to which protein product of the gene the claims are directed. For this reason, the claim fails to delineate the metes and bounds of the subject matter that is regarded as the invention with the clarity and particularity necessary to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

(e) Claims 60 and 61 are vague and indefinite because the claims recite the processes are intended for use in "classifying cancers", and though the processes comprise the step of "classifying those cancers from patients whose body samples show amplification or increased expression of said MAC117 gene or abnormal expression of the protein product of said MAC117 gene as being correlated with

amplification of the MAC117 gene or increased expression of the protein product of the MAC117 gene", it is not evident what attributes or features of the cancers are "correlated" with gene amplification or increased expression of the gene product. A "correlation" is a reciprocal relation between two or more things. So, here, it is not understood how the cancers are actually *classified* upon practice of the claimed processes because it is not evident what relationship must be identified; but if it cannot be known whether or when the objective is met, it would seem that the claims necessarily fail to clearly and particularly point out the subject matter that is regarded as the invention, so as to permit the skilled artisan to know or determine infringing subject matter, and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

(f) Claim 69 is too vague and indefinite to satisfy the requirement for clarity and particularity set forth under 35 U.S.C. § 112, second paragraph, for the following reasons:

The claim is directed to an omnibus subject matter, as it is apparently directed to an active step (i.e., detecting a MAC117 gene), rather than a useful process having any one particular objective or purpose, which at first glance may conceivably be performed during any number of a vast plurality of objectively different processes.

Indeed, the specification discloses a process for diagnosing cancer in a patient, which comprises detecting a MAC117 gene and determining if the gene is amplified, rearranged and/or overexpressed, but the claimed process of detecting a MAC117 gene is not disclosed as having any particular purpose, in and of itself, and appears to be described as only an integral part or active step of other processes disclosed in this application.

To satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, the claims *must* define the metes and bounds of the subject matter that is regarded as the invention by Applicant with the clarity and particularity necessary to permit the skilled artisan to know or determine infringing subject matter.

What is the actual purpose or objective of practicing the process that is regarded as the invention? How and when not might the gene be detected by hybridizing nucleic acid with a nucleic acid probe of the gene without infringing the claim?

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claim 69 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

What is the actual "real-world" purpose or objective of practicing the invention? How is it to be used in a manner that would immediately benefit the public, and to what specific aim or objective?

Inasmuch as the claimed invention has no requisite objective or purpose, apart from the detection of a gene, and has no apparent specific and substantial utility, in and of itself, the sufficiency of the disclosure to reasonably enable the skilled artisan to practice the invention, or any objective process comprising the invention as an integral and active step cannot be assessed.

Furthermore, because the claimed invention has no requisite objective or purpose, apart from the detection of a gene, the claims merely serve as an invitation to elaborate a "real-world" use for the invention, or to develop a useful process comprising the active step of detecting the gene. However, any need to further elaborate or develop a utility for the claimed invention, which would satisfy the requirement set forth under 35 U.S.C. § 101, would constitute a need to perform undue and/or unreasonable experimentation.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue”. These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

20. Claims 61, 68, and 69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a “new matter” rejection.

(a) Claims 61 and 68 are directed to methods of *classifying* cancers.

Claim 61 was added by the amendment filed August 12, 1993. At page 3 of that amendment Applicant has remarked that specification "clearly supports that MAC117 amplification can be detected and used to classify those cancers having amplification".

Thus, it would appear that it is Applicant’s position that because the specification shows that the gene encoding the 185 kDa polypeptide is amplified in certain breast

cancer cells, the specification must adequately support a claim directed to a method of classifying cancers.

It is argued however that since the specification shows that the gene encoding the 185 kDa polypeptide is amplified in certain breast cancer cells, the specification might adequately support a claim directed to *a method of determining if the gene is amplified in breast cancer cells*, but it would not support a claim directed to a method of classifying cancers.

Claim 68 was added by the amendment filed May 3, 2006; and at page 4 of that amendment Applicant has remarked that written support for the language of claim 68 is found in the specification at page 5, lines 3-6, and page 26, lines 23-25, if not also elsewhere.

The disclosure at page 5 reads as follows: "It is a still further object of the present invention to provide nucleic acid probes and/or antibody reagent kits capable of detecting said gene or a product thereof."

The disclosure at page 26 reads: "Having the knowledge of the gene allows preparing specific nucleic acid probes to detect the gene described here or its mRNA product."

Neither disclosure appears to provide written support for the claimed process of classifying cancers.

In fact, no where in the specification, as originally filed, are such methods expressly described.

Given the apparent absence of any express description of the claimed processes of *classifying* cancers, it is submitted that it is not evident what subject matter is actually regarded as the invention because, for example, it cannot be ascertained what objective must actually be met by "classifying" cancers or when that objective would be met. Presumably the claimed invention is not just a method of determining if the gene encoding the 185 kDa protein described in the application is amplified. Though this is arguably an issue better addressed under the provisions of 35 U.S.C. § 112, second paragraph, because it is not evident to what intent or purpose the invention is used, it is

really not possible to determine if there might be any implied or inferred support found within the disclosure.

Even so, since the specification does not describe the "classification" of cancers by the active process that is recited in the body of the claims, it seems unlikely that it would should be found to provide adequate written support, implied or otherwise, for the claimed methods of doing so.

Therefore, until established otherwise, it appears that the addition of claims 61 and 68, directed to methods of classifying cancers, has introduced new concepts, which might not be adequately supported by the specification, as originally filed; in which case the addition of those claims violates the written description requirement set forth under 35 U.S.C. § 112, first paragraph. This issue might be remedied if Applicant were to point to specific disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the claims.

(b) Claim 69 is drawn to a method of detecting a MAC117 gene comprising hybridizing nucleic acid with a nucleic acid probe of the gene.

Claim 69 is not an original claim, but was added by the amendment filed May 3, 2006. At page 4 of that amendment Applicant has asserted written support for the claim is found in the specification, as originally filed, at page 5, lines 3-6, and at page 26, lines 23-25.

The disclosure at page 5 reads as follows: "It is a still further object of the present invention to provide nucleic acid probes and/or antibody reagent kits capable of detecting said gene or a product thereof."

The disclosure at page 26 reads: "Having the knowledge of the gene allows preparing specific nucleic acid probes to detect the gene described here or its mRNA product."

Contrary to Applicant's assertion, however, it does not appear such disclosures provide adequate written support for the *breadth* of subject matter to which the instant claims are directed.

Again, claim 69 is drawn to a method of detecting a gene; however, the claim recites no intended use or purpose, apart from the detection of the gene.

Accordingly, this new claim is not directed to any of the originally disclosed and/or claimed processes that comprise the step of detecting the gene, but rather to an active step that might be comprised within any number of a very large plurality of objectively different processes, few of which might be described in the instant specification.

Yet, no where in the specification does it appear the claimed invention (i.e., of detecting a MAC117 gene comprising hybridizing nucleic acid with a nucleic acid probe of the gene) is described, in and of itself.

In fact, the only recitations of the term "detecting", which appear in the specification, are in descriptions of the products that are useful for detecting the gene and/or abnormalities thereof, or in descriptions of the processes that involve detection of the gene.

For these reasons, it appears the addition of new claim 69 has introduced new concepts not adequately embraced by the contents of the specification, including the claims, as originally filed; and as such, addition of claim 69 has violated the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

This issue might be remedied if Applicant were to point to other particular disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the instant claims.

21. Claims 60, 61, 68, and 69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines

for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In this instance, claim 60 is directed to a process for diagnosing any of a genus of "human cancers" in a patient by detecting amplification, rearrangement or increased expression of "a MAC117 gene" in a tissue or tumor cell sample from said patient; whereas claims 61 and 68 are directed to processes for classifying cancers by detecting amplification or increased expression of "a MAC117 gene" in a tissue or tumor sample containing cells from a patient diagnosed with cancer or alternatively by detecting abnormal expression of a protein product of said MAC117 gene; and claim 69 is directed to a process for detecting "a MAC117 gene".

As such, each of claims 60, 61, 68, and 69 is directed to "a MAC117 gene", which is necessarily amplified, rearranged, or overexpressed in a tissue or tumor cell sample, so as to be indicative of the presence of human cancer in a patient from whom the sample is acquired.

Notably the term "MAC117 gene" is not expressly defined in the specification, but is presumed to encompass a plurality of DNA molecules having different nucleotide sequences, including, for example, any gene comprising at least part of the nucleotide sequence recited in claim 1 (now canceled).

As might be expected there are a *very* large number of structurally and functionally disparate genes comprising at least part of the nucleotide sequence that is recited in claim 1.

It is submitted that the vast majority of such structurally and functionally disparate genes are not expected to have or bear any relationship to the gene that is described in this application as amplified and overexpressed in certain breast cancer cell lines (e.g., SK-BR-3).

Accordingly the claims are broadly but reasonably directed to process for diagnosing any of a genus of "human cancers" in a patient by detecting amplification, rearrangement or increased expression of any of a very large number of structurally and functionally dissimilar genes in a tissue or tumor cell sample from said patient.

In contrast to the breadth of claims 60, 61, 68, and 69, the specification merely describes the amplification and/or overexpression of a gene comprising the entirety of the nucleotide sequence recited in claim 1, which encodes a polypeptide having a molecular weight of about 185 kDa, in certain breast cancer cell lines; see, e.g., Figures 1 and 7.

The substantially more limited description of the particular gene comprising the entirety of the nucleotide sequence recited in claim 1 and encoding a polypeptide having a molecular weight of about 185 kDa would not reasonably convey to the skilled artisan that Applicant had possession of any of the claimed processes that comprise detecting amplification, rearrangement, or increased (abnormal) expression of any "MAC117 gene".

Just as the vast majority of the structurally and functionally disparate “MAC117 genes” are not expected to have or bear any relationship to the particularly described gene, it is also expected that few of such gene will be amplified and/or overexpressed in cancer cells, so as to suitable for use as diagnostic markers.

Then, even if the claims were substantially more limited to a gene comprising the entirety of the nucleotide sequence recited in claim 1, it is still submitted that the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed for the following reasons:

The nucleotide sequence recited in claim 1 is described as that of a fragment of a cloned DNA molecule produced by cleavage of the molecule with the restriction enzymes Eco RI, Acc I and Nco I[4]; thus the sequence recited in claim 1 is but a mere portion of the entirety of the coding sequence of the cloned gene.

As such, even if the claims were directed to genes comprising the nucleotide sequence recited in claim 1, the genes would not necessarily comprise the nucleotide sequence of the cloned gene, which is amplified and/or overexpressed in certain breast cancer cell lines.

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[4] See Figure 1 and the brief description of the figure at page 5 of the specification.

Figure 1 of the specification shows that the nucleotide sequence recited in claim 1 (i.e., the nucleotide sequence of the fragment of the cloned gene) comprises at two exons encoding at least part of a putative polypeptide having the amino acid sequences also depicted in Figure 1; thus the nucleotide sequence recited in claim 1 does not encode a full-length polypeptide.

As such, even if the claims were directed to genes comprising the nucleotide sequence recited in claim 1, the genes would not necessarily comprise the nucleotide sequence of the cloned gene that encodes a polypeptide of 185 kDa, which is recognized by the antibody described in this application.

Given the fact that the "MAC117 genes" encompassed by the claims have such widely varying structures and functions, it is submitted that the gene comprising the entirety of the nucleotide sequence recited in claim 1 and encoding a polypeptide having a molecular weight of about 185 kDa, which is described in this application, is not representative of the genus, as a whole, as the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the genes, even given the description of a restriction map of the cloned gene and part of its nucleotide sequence.

This is, in part, because the genes to which the claims are directed need not have or share any of particularly identifying structural features of the cloned gene, which account for any particularly identifying functional features of either the gene or its product, which are also shared by members of the claimed genus.

Applicant is reminded that “generalized language may not suffice if it does not convey the detailed identity of an invention.” *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

In this instance, there is no language that adequately describes at least a substantial number of members of the genus of genes to which the claims are directed, which are amplified, rearranged or overexpressed in cancer, so as to be useful in diagnosing the disease. A description of what a material must do, rather than of what it is, does not suffice to describe the claimed invention.

Again the gene, which is only described in part as comprising the nucleotide sequence recited in claim 1 and/or encoding the 185 kDa polypeptide, is not representative of the genus, as a whole, since members of the genus have widely varying structures and functions.

Furthermore, it aptly noted that the courts have established that the disclosure of a partial structure without additional characterization of the product may not be sufficient to evidence possession of the claimed invention. See, e.g., *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd*, 927 F.2d at 1206, 18 USPQ2d at 1021 ("A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e.g., encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated.") (citations omitted).

Furthermore, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

First of all, one cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. Apart from the gene encoding the 185 kDa polypeptide, which is amplified and/or overexpressed in certain breast cancer cell lines, it seems improbable that Applicant conceived at least a substantial number of the other members

of the claimed genus "MAC117 genes" that are amplified, rearranged, or overexpressed in human cancers, including those that encode, for example, any of the structurally and/or functionally disparate isoforms of the 185 kDa polypeptide that have since been described in the art.

Nevertheless, here, any alleged conception fails, not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor's idea of the invention. See *Burroughs Wellcome Co. v. Barr Laboratories Inc.*, 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994). Reduction to practice in effect provides the only evidence to corroborate conception (and therefore possession) of the invention.

Notably, too, Guidelines (*supra*) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Guidelines further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient

to show that Applicant had possession of the claimed invention at the time the application was filed.

For additional clarity it is appropriately noted that the structure of a gene cannot be instantly envisioned or predicted, even given a full description of a mRNA molecule, which is the transcript of the gene, or the cDNA molecule derived therefrom. A gene contains *introns*, or intervening sequences that are dispersed among the exons encoding the transcription and translation products of the gene. Introns do not provide coding information that is utilized in producing the RNA transcript or polypeptide encoded by a gene, and the polynucleotide sequences of the introns are excised during maturation of the RNA transcript, or mRNA so that only the polynucleotide sequences of the spliced exons remain. Therefore, the artisan cannot deduce the structure of an intron, or of a gene containing an intron given only the polynucleotide sequence of an mRNA molecule, or cDNA derived therefrom. In addition, a gene comprises polynucleotide sequences at either end, i.e., the 5' and 3' ends, which contain regulatory information. For example, the promoter of the gene is most commonly positioned at the 5' end of the gene and regulates the transcription of the gene. Because the polynucleotide sequence of the promoter of a gene is not transcribed, its structure cannot be surmised given only the polynucleotide sequence of the RNA transcript of the gene. Other regulatory sequences are positioned at the 5' and 3' ends of the gene, which encode portions of the RNA transcript, which are not translated.

As such, it is not possible to work backward from the known structure of a cDNA molecule, for example, to derive the unknown structure of the corresponding gene, which encodes the same polypeptide as the cDNA; and therefore, the structures of naturally occurring genes with regulatory elements, untranslated regions, and introns and exons can only be determined empirically. This position is supported, for example, by the disclosures of Harris et al. *(J. Am. Soc. Nephrol.* 1995; **6**: 1125-1133), Ahn et al. (*Nature Gen.* 1993; **3**: 283-291); and Cawthon et al. (*Genomics* 1991; 9: 446-460).

In this particular case, only a portion of the nucleotide sequence of a single "MAC117 gene" is disclosed. As shown in Figure 1, it appears that this sequence comprises two exons and one intron, but is otherwise incomplete. Thus, the

specification fails to fully describe the particularly identifying structural attributes of the gene.

M.P.E.P. § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ".

In addition, Applicant is reminded that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Accordingly, it is submitted that in the absence of a detailed description of at least a substantial number of the members of genus of "MAC117 genes", one skilled in the art would not reasonably conclude that Applicant had possession of the claimed invention at the time the application was filed.

It is however important to note that the claims are directed, not to a product, but to a process of diagnosing cancer in patients, processes of classifying cancer, and processes of detecting a gene. Without the gene it is not possible to practice the claimed inventions, so as to achieve the claimed objectives.

Similarly it is not possible to practice the claimed invention, so as to achieve the claimed objective, if it is not known which types of cancer may be diagnosed by determining that the nucleic acid derived from a tissue or tumor cell contains an amplified, rearranged, or overexpressed MAC117 gene - but which types of cancer are those? As further discussed in the following paragraphs, it is apparently not every type

of cancer that is associated with the amplification, rearrangement or overexpression of a MAC117 gene.

It would seem that the specification fails to describe with any of the requisite clarity and particularity the other types of cancer that may be diagnosed using the claimed process; and moreover, it fails to describe those types of cancer which may not.

It is aptly noted that the specification discloses that amplification of a MAC117 gene was only detected in some of the breast cancer cell lines analyzed; for example, amplification was detected in SK-BR-3 cells, but not in ZR-75-1 cells; see, e.g., Figure 8 *B*. Thus, it appears that only a portion of breast cancers are associated with amplification of a MAC117 gene.

Furthermore, although the specification describes certain breast cancer cell lines, such as SK-BR-3 and ZR-75-1 as containing an amplified and/or overexpressed MAC117 gene, it appears not to describe a single example of a cancer cell characterized as having a gene rearrangement. Instead the specification only vaguely discloses that the abnormalities of a MAC117 gene that might be detected in cells include gene rearrangement, which might be indicated by aberrantly migrating bands in hybridization based assays (page 29, lines 13-16); but since specification also expressly discloses that aberrantly sized mRNA was not detected in any cell (page 22a, lines 18-20), it is submitted that the skilled artisan would not reasonably conclude that Applicant had possession of the claimed process comprising detecting rearrangement of a MAC117 gene at the time the application was filed.

Turning to a slightly different issue now, in further contrast to the claims, the only gene product (i.e., polypeptide) described in this application with any clarity and particularity is the 185 kDa polypeptide that is presumably encoded by the gene amplified and/or overexpressed in certain breast cancer cell lines; see, e.g., Figure 7.

As shown in Figure 7 *A*, this 185 kDa polypeptide is produced by the breast cancer cell line SK-BR-3; it however not apparent produced by another cell line, namely A431, which is derived from a different type of cancer, a vulva epidermoid carcinoma.

Thus, it is importantly noted that the gene encoding the 185 kDa polypeptide may not be expressed in all types of cancer, since it was not seen in a cell line derived from

a vulva epidermoid carcinoma; yet, the claims are directed to a process for diagnosing any of a genus of "human cancers", and not necessarily breast cancer.

The absence of the 185 kDa polypeptide in A431 epidermoid carcinoma cells suggests there is no basis for Applicant's assertion that the detection of amplification, rearrangement, or increased expression of a "MAC117 gene" in a sample of tissue or tumor acquired from a patient provides a diagnostic indication that the patient has any type of cancer.

Instead it is submitted that at best the specification might show that there is a relationship between amplification and/or overexpression of the gene encoding the 185 kDa polypeptide in the cells contained in a sample of breast tissue from a patient and the presence of breast cancer in the patient.

Otherwise, however, the specification would fail to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention because it is apparent that not all types of cancer are associated with the amplification and/or overexpression of the gene encoding the 185 kDa polypeptide and there is no disclosed basis for reliably predicting whether any other types of cancer, apart from breast cancer, might be diagnosed upon detecting amplification and/or overexpression of the gene encoding the 185 kDa polypeptide in samples of breast tissue acquired from patients.

Yet, it is further noted that although it appears the 185 kDa polypeptide is produced by both SK-BR-3 and ZR-75-1 breast cancer cell lines, it appears that Figure 7 *B* shows that little, if any, of the polypeptide is produced by the MCF-7 breast cancer cell line[5]; if so, the specification would suggest that the expression of the gene encoding the 185 kDa polypeptide may not be a general attribute of breast cancer, which will be useful in diagnosing the disease, but may perhaps be a marker of some as then yet poorly defined subset of breast cancers.

So, again, apart from the 185 kDa polypeptide, the specification fails to describe any other protein encoded by any of the "MAC117 genes" to which the claims are directed, including, for example, any of the other isoforms of the 185 kDa polypeptide

that have since been described as the products of alternatively spliced transcripts of a common gene. In particular, the specification fails to describe the structurally and functionally different isoforms described by Scott et al. (*supra*), Aigner et al. (*supra*), and Doherty et al. (*supra*).

Applicant's failure to detect any of the other isoforms encoded by the gene that is amplified and/or overexpressed in certain breast cancer cell lines (e.g., SK-BR-3 and ZR-75-1) may have stemmed, in part, from the fact that the antibody used in the analysis binds to an intracellular portion of the 185 kDa isoform, which the other isoforms lack. Scott et al. (*supra*), for example, discloses that the 100 kDa isoform encoded by a "MAC117" appears to arise by alternative splicing in that the 5' 2.1 kb of the encoded transcript is identical to that of a 4.6-kb transcript but the 3' end of the truncated transcript diverges 61 nucleotides before the receptor's transmembrane region, reads through a consensus splice donor site containing an in-frame stop codon, and contains a poly(A) addition site (abstract). Accordingly, Scott et al. disclosed this alternatively spliced transcript of the gene would be expected to produce an isoform containing only the extracellular ligand binding domain of the larger 185 kDa isoform; see, e.g., the abstract. If so, the antibody that Applicant has described, which was raised using a peptide having the amino acid sequence of amino acids 35-49 of the sequence recited in claim 4 (now canceled)[6], and which the specification discloses recognizes a portion of the putative intracellular tyrosine kinase domain of the 185 kDa polypeptide[7], is not expected to specifically bind to the 100 kDa isoform, or any other isoform lacking the epitopes contained in the peptide using to generate the antibody. Therefore, Applicant's disclosure of the 185 kDa isoform alone, and the description of an antibody recognizing only an intracellular portion of this isoform, would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention, which comprises the detection of abnormal levels of any of a plurality of proteins that are gene products of a "MAC117 gene".

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[5] At page 22d, lines 20-22, the specification discloses that the 185 kDa polypeptide was not detected in MCF-7 cells.

[6] See, e.g., page 26, lines 14-16, of the specification, as originally filed.

Furthermore, since these other gene products have different functions, which include the inhibition of tumor cell proliferation[8], are apparently encoded by the same gene that is amplified, rearranged or overexpressed in certain breast cancer cell lines, it seems reasonable to question whether the detection of amplification, rearrangement, or increased expression of a "MAC117 gene" in a sample of tissue or tumor acquired from a patient provides a reliable diagnostic indication that the patient has breast cancer. Perhaps the only true indication that the sample acquired from a patient contains breast cancer cells is a relatively greater abundance of the 185 kDa isoform, as compared to the level that occurs in normal breast cells. This might be the case if, for example, it turns out that the ratio of the levels of the 185 kDa isoform and any of the other isoforms, which appear to inhibit tumor cell proliferation, is important in developing breast cancer. However, since it appears that MCF-7 breast cancer cells do not produce detectable levels of the 185 kDa polypeptide[9], the protein might not be expected to serve as a suitable diagnostic marker.

So is the "MAC117 gene" encoding the 185 kDa polypeptide a suitable marker for use in diagnosing breast cancer, or any other types of cancer?

The specification appears to have only shown an analysis of the gene's expression in a relatively few number of breast cancer cell lines, and then it appears that gene is not overexpressed in some of those cell lines. Again, MCF-7 cells did not produce detectable levels of the 185 kDa protein (Figure 7 *B*); and then only 50% of the cell lines analyzed produced increased levels of a 5 kb transcript, which allegedly encodes the protein (page 22a, lines 16-18).

Furthermore, as previously mentioned, the specification shows that the gene encoding the 185 kDa polypeptide was not amplified or overexpressed in A431 vulva epidermoid carcinoma cells; so the gene may not be amplified or overexpressed in other types of cancer.

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[7] See, e.g., page 22b, lines 6 and 7, of the specification, as originally filed.
[8] See, e.g., the disclosure by Aigner et al.
[9] See, e.g., page 22b, lines 17-19, of the specification, as originally filed.

Even in instances where carefully controlled experiments establish the that a genetic marker is differentially expressed by cancer cells, compared to matched normal cells of the same tissue, the determination of the presence or expression of some tumor markers has proven to be ineffective in enabling an accurate and reliable diagnosis of all stages of cancer. Ward (*Developmental Oncology* 1985; **21**: 91-106) teaches not all markers can be reliably used in primary diagnosis; see, e.g., pages 96 and 97. Ward teaches that a number of tumor-associated markers are, in fact, diagnostically unreliable. Rather, Ward teaches some markers are more useful as guides in monitoring the efficacy of treatment modules for malignant disease; see, e.g., pages 98 and 99.

In this instance, the specification describes amplification and/or overexpression of a "MAC117 gene" encoding a 185 kDa polypeptide in some, but not all breast cancer cell lines; it does not however establish that the gene is suitable for use as a marker in diagnosing early stage, primary breast cancer.

It is therefore pertinent to note that Yokata et al. (*Lancet*. 1986 Apr 5; 1 (8484): 765-767) describes a case in which the gene was amplified in a metastasis of a breast tumor, but not in either the primary tumor or the matched normal breast tissue; see entire document (e.g., page 766, column 2).

It is submitted that this finding described by Yokota et al. (*supra*) constitutes strong factual evidence that though the specification describes amplification and/or overexpression of a "MAC117 gene" encoding a 185 kDa polypeptide in some breast cancer cell lines, such a showing does not reasonably convey that Applicant established that the gene is suitable diagnostic marker for use in diagnosing *early stage*, primary breast cancer.

Critchfield (*Disease Markers* 1999; **15**: 108-111) teaches: "Indeed, to truly benefit society, the clinical value of the gene must be established" (page 109, column 1). Following the discovery of a novel gene, Critchfield discloses the process of determining whether the gene can be used successfully as a biomarker for diagnosis is lengthy and involved. Similarly, the discovery of a possible association between the expression of a gene and cancer would be followed by an equally long and arduous

process by which it is determined if the over- or under-expression of the gene in cancer cells, relative to its normal level of expression in normal cells, can be used to diagnose or detect cancer. Sidransky (*Science* 1997; **278**: 1054-1058) teaches this process must first establish the reliability of a novel diagnostic method, which measures the expression of a biomarker, through feasibility studies; then, after the reliability of the technique is established, its sensitivity and specificity must be assessed in formal clinical trials before the technique can be used with a reasonable expectation of success (page 1055, columns 1 and 2). Tockman et al. (*Cancer Research* 1992; **52**: 2711s-2718s) teaches considerations necessary in bringing a cancer biomarker (intermediate endpoint marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to risk assessment, diagnosis, and/or prognosis of any type of cancer. Tockman et al. teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence, and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated can be used for population screening (page 2713, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate endpoint marker (page 2714, column 1). Clearly, prior to the successful application of newly described markers, these must be validated against acknowledged disease end points; and, the marker predictive value must be confirmed in prospective population trials (page 2716, column 2).

In truth, given benefit of many years of continued investigations into the value of this "MAC117 gene" encoding the 185 kDa polypeptide, it would appear that the gene is better used as a prognostic marker, rather than a diagnostic marker of various different types of cancer, including in particular breast cancer.

Slamon et al. (*Science*. 1987 Jan 9; **235**: 177-182), for example, describes a relatively early study that shows that the incidence of amplification of the "MAC117 gene" encoding the 185 kDa polypeptide in breast cancer correlated with different clinical parameters, such that amplification of the gene was found to be a significant predictor of overall survival and time to relapse in the patients; see entire document (e.g., the abstract).

Ongoing work has continued to build upon such early results to redefine the significance of amplification and/or overexpression of the "MAC117 gene" encoding the 185 kDa polypeptide in breast cancer, as well as other types of cancer. Kim et al. (*J. Korean Med. Sci.* 2008 Jun; **23** (3): 414-420), for example, recently published the results of a study showing that the clinical significance of the amplification of the gene was confined to advanced breast cancer, as amplification of the gene was an independent prognostic factor only in stage III disease; see entire document (e.g., the abstract).

Thus, while it seems that this "MAC117 gene" encoding the 185 kDa polypeptide has value as a prognostic marker, there appears very little to suggest that the amplification and/or overexpression of the gene is an apt diagnostic marker.

In addition to the reasons already discussed in the preceding paragraphs, it seems also that relatively early studies showed that amplification and/or overexpression of a "MAC117' gene is not associated with all types of cancer, but may only be related to adenocarcinomas.

Besides finding a case in which the gene was amplified in a metastasis, but not a primary breast tumor that gave rise to the metastasis, which suggests amplification of the gene is not a suitable marker of early stage disease, Yokota et al. (*supra*) describes their discovery that the gene is amplified only in a proportion of adenocarcinomas of various different tissues, but not in any other type of cancer; see entire document (e.g.,

page 766, column 2). More particularly, Yokota et al. discloses that amplification was detected in a proportion of adenocarcinomas of the stomach, kidney, and breast, but not in adenocarcinomas of the lung, caecum, colon, rectum, and ovary, or in any of a number of different squamous cell carcinomas, sarcomas, leukemias, or lymphomas (page 766, the table in column 1).

Noteworthy is the disclosure at page 22 of the specification, which suggests the diagnostic value of "MAC117 gene" amplification should be expected because there is a precedent for the identification of gene related to known oncogenes on the basis of their amplification in human tumors since there is a high degree of amplification of N-myc, for example, in certain malignancies (lines 1-7).

Such an expectation however may not have been reasonable given the unpredictable nature of the art; and not inconsistently, Yokota et al. (*supra*) pointedly concludes that unlike the c-myc gene, which is amplified in a variety of different types of tumors, amplification of the "MAC117 gene" appears restricted to certain adenocarcinomas (page 766, column 2).

Addressing now a different issue, claims 60, 61, and 68 are directed to a process of diagnosing or classifying cancers in patients by detecting abnormal expression of a protein, which is encoded by a "MAC117 gene", in a body sample acquired from the patient using an immunoassay.

It appears that written support for the concept of using such a body sample is found only in original claim 8 (now canceled), which recites a step of "detecting abnormal expression of the protein product of the gene of Claim 1 by reacting a body sample of a human suspected of said cancer with antibodies of Claim 5". As noted in the above objections to the specification, there is however no antecedent basis for such claim language found in the disclosure.

As evidenced by the declaration of Matthias H. Kraus under 37 C.F.R. § 1.132 filed June 17, 1996, the term "body sample" is not used solely to refer to a sample of tissue or tumor, since the body sample may instead be a sample of serum or effusion, or perhaps any other sample that might be acquired from the body of a patient, other than tissue or tumor cells.

In contrast to the evident breadth of the term "body sample", as it is used in the context of the language of the claims, the specification appears to describe only samples of tissue or tumor; it does not describe the use of samples of sera, effusions, or any other bodily component that might be acquired from the body of a patient, other than tissue or tumor cells.]

Moreover, the specification fails to describe the presence of the 185 kDa polypeptide, or any isoform thereof, which is also encoded by a "MAC117 gene" in the serum or any other bodily fluid of patients with breast cancer or any other type of cancer. Instead the specification merely shows the presence of elevated levels of the polypeptide in the cellular extracts of certain breast cancer cell lines; see, e.g., Figure 7 *B*; and page 22b, lines 4-15, of the originally filed specification.

The art teaches that the presence of a tumor-associated antigen in the serum or other bodily fluid of the patient afflicted by cancer cannot be predicted solely upon the basis that the antigen is abnormally expressed at relatively abundant levels by the cancer.

Support for this position is found, for example, in the teachings of Roessler et al. (*Mol. Cell. Prot.* 2006; **5** (11): 2092-2101). Roessler et al. teaches that of five proteins identified as elevated in tissue samples obtained from individuals with colorectal cancer only one of these proteins could be shown to be elevated in serum samples obtained from individuals with colorectal cancer; see entire document (e.g., page 2099, right column). Additionally, Roessler et al. (*Clin. Can. Res.* 2005; **11** (18): 6550-6557) teaches, while proteins may be elevated in tissue samples obtained from individuals with colorectal cancer, "which of the cancer-associated proteins found in tumor tissue that eventually will be present in serum or plasma cannot be predicted *a priori*"; see entire document (e.g., page 6556, right column). Thus, according to Roessler et al., development of highly sensitive immunoassays for each candidate marker and subsequent assessment of serum/plasma samples is mandatory (page 6556, right column). Similarly, Zolg et al. (*Mol. Cell. Prot.* 2004; **3** (4): 345-354) discloses, upon commenting on whether proteins identified as elevated in cancer tissue screens will also be elevated in liquid samples obtained from individuals, "[an] inherent risk in the tissue

approach is the fact that the candidate marker identified in e.g., tissue cannot later be detected in peripheral fluid such [as] serum"; see entire document (e.g. page 347, right column).

In this instance, the specification fails to describe with any of the requisite clarity and particularity the presence in the serum or any other bodily sample, apart from certain breast tumor cells, of the gene product of an amplified or overexpressed "MAC117 gene".

The declaration under 37 C.F.R. § 1.132 by Matthias H. Kraus, filed June 17, 1996, states that it is believed that "increased expression of the MAC117 gene can be detected in body samples other than tissue or tumor cells" (page 1, item 2). However, the declaration states that this belief is based upon the disclosure of a manuscript published after the filing date sought by the Applicant, namely that of Leitzel et al. (*J. Clin. Oncol.* 1992 Sep; **10** (9): 1436-1443), which describes the presence in the serum and effusions of a proportion of breast cancer patients a soluble protein that appears to be the product of a "MAC117 gene". There is no suggestion that Applicant had knowledge of the results disclosed in this later published report at the time the application was filed; and as such it appears that Applicant would not have had any such basis for believing that "increased expression of the MAC117 gene can be detected in body samples other than tissue or tumor cells" as of the filing date of this application.

Nevertheless, it is aptly noted that the soluble protein described by Leitzel et al. has a molecular weight of about 105 kDa, not 185 kDa. Again, the only protein described with any clarity and particularity in this application as the product of an amplified and/or overexpressed "MAC117 gene" in cancer cells is a protein having a molecular weight of about 185 kDa.

Then, too, it is aptly noted that the secreted, soluble protein of about 105 kDa, and which was detected by Leitzel et al. using antibodies that specifically bind to the extracellular portion of the 185 kDa isoform, is likely the same isoform described by others (e.g., Aigner et al. (*supra*)).

As previously explained, Aigner et al. (*supra*) discloses that this isoform acts as an endogenous inhibitor of tumor cell proliferation, since enforced expression of a cDNA encoding this isoform in MCF-7 breast cancer cells decreased spontaneous proliferation of the cells and inhibited heregulin-mediated soft agar colony formation; see, e.g., the abstract. In addition, Aigner et al. teaches that levels of the transcript encoding this isoform were found to decrease toward a progressive lose of expression in more advanced gastric tumors; see, e.g., the abstract.

In view of the disclosure of Aigner et al., it is submitted that the presence of a soluble isoform encoded by the "MAC117 gene" encoding the 185 kDa isoform may not be indicative of the presence of cancer in a patient since its expression by cancer cells diminished with disease progression and it functions to inhibit the growth of tumor cells.

Yet, Kath et al. (*Ann. Oncol.* 1993 Aug; **4** (7): 585-590) pointedly teaches that the presence of the protein in the serum of patients with breast cancer may be indicative of advanced, metastasized disease, but not of primary breast cancer; see entire document (e.g., the abstract). Moreover, Kath et al. discloses that the protein was not detected in the serum of any of 30 patients with primary breast cancer (abstract).

Given such disclosures, it would seem that the significance of the presence of any soluble protein in the serum, for example, of patients cannot be predicted solely upon the belief that it is secreted into the serum; and such reasoning suggests that the specification would fail to convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Then, with particular regard to claim 69, which is directed to a method of detecting a MAC117 gene, since the claimed invention achieves no requisite effect, and has no specific objective or purpose, apart from the detection of a gene, it appears that the claimed invention is merely *an active step* of which some other undisclosed or unclaimed process is comprised, and which has not been described with the requisite particularity by the instant claims to satisfy the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Therefore, Applicant is again reminded that "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Furthermore, "[r]egardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004).

Because the claimed invention has no objective or purpose, apart from the detection of a gene, it seems the claim would serve as a mere invitation to the artisan to develop a useful process comprising the active step of detecting a MAC117 gene.

However, while it might be plausible to develop useful processes that achieve specific objectives or purposes, which comprise the active step of detecting a MAC117 gene, Applicant is reminded that the written description provision of 35 U.S.C. § 112, first paragraph, is severable from its enablement provision. An adequate written description requires more than a mere statement that it is the invention.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

22. Claims 60, 61, and 68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue”. These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the above rejection of the claims as failing to satisfy the written description requirement, it is evident that the claimed invention could not be used without undue and/or unreasonable experimentation.

Applicant is therefore reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to determine which types of cancer, if any, might be diagnosed (or classified) by determining if "a MAC117 gene" is amplified, rearranged or overexpressed.

Though the specification describes the amplification of a gene in one breast cancer cell line, it describes the lack of amplification of the gene in another breast cancer cell.

Though the specification describes the overexpression of a gene in a breast cancer cell line, it describes the lack of expression in another.

Yet, the claims are not limited to processes for diagnosing breast cancer, but are instead directed to processes for diagnosing any of a genus of human cancers.

Despite this fact, the specification teaches that the gene that is amplified and/or overexpressed in certain, but not all breast cancer cells is neither amplified nor overexpressed in an epidermoid carcinoma.

Then, as evident in view of later published studies, it would seem that the gene is only associated with a proportion of adenocarcinomas, but few if any other types of cancer.

Moreover, it appears that the amplification and/or overexpression of the gene in breast cancer may not be diagnostic of early stage disease, but is instead better suited for use as a prognostic marker predictive of relapse and overall survival.

The specification does not describe any gene rearrangement, nor does it attribute the presence of any cancer to the occurrence of a gene rearrangement.

Given the state of the art, as well as its unpredictable nature, especially in view of the results of studies published after the filing date sought by Applicant, it is submitted that the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

However, even at about the time the application was filed, it seems that there was considerable evidence that the claimed invention could not be used to diagnose any given type of cancer.

Coussens et al. (*supra*), for example, reports that though several embryonic tumors expressed large amounts of a 4.8 kb transcript encoding a 185 kDa polypeptide, levels of the transcript did not exceed those of normal fetal tissue; see entire document (e.g., page 1136, column 3).

Such results indicate that the gene is only overexpressed in a certain proportion of cancers and that it cannot be predicted which types of cancer will or will not overexpress the gene. Cancer cells overexpressing the gene can only be identified by empirically testing the expression of the gene.

All such reasoning aside, it is additionally noted that claim 60, for example, recites, "by hybridizing nucleic acid derived from a tissue or tumor cell sample of said patient with a nucleic acid probe of the MAC117 gene". If one were to presume the nucleic acid derived from the sample is *chromosomal DNA*, it is reasonable to question how the process might identify a sample containing cells overexpressing the gene. This is because it is expected that each cell comprises at least an allele of the gene; so therefore it would seem that such a process might not distinguish a sample comprising a cancerous cell from a sample containing only normal cells.

The specification describes the application of such a process for detecting overexpression of a gene, but in that example it is not chromosomal DNA that is utilized but rather RNA. Chromosomal DNA is utilized in identifying a sample comprising a cell in which the gene has been amplified, but the process is not described as useful in identifying cells that produce increased levels of the gene product.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

23. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

24. Claims 60, 61, 68, and 69 are rejected under 35 U.S.C. 102(b) as being anticipated by King et al. (*Science*. 1985 Sept 6; **229**: 974-976).

Herein, claims 60, 61, and 68 are drawn to a process comprising determining whether a MAC117 gene is amplified in a tissue or tumor cell from a patient by hybridizing nucleic acid derived from the tissue or tumor cell with a nucleic acid probe of the gene; and claim 69 is drawn to a process of detecting a MAC117 gene by hybridizing nucleic acid with a nucleic acid probe of the gene.

King et al. teaches a process comprising detecting a gene and determining that the gene is amplified in the human mammary carcinoma cell line, MAC117 by hybridizing nucleic acid derived from the cells with a nucleic acid probe of the gene; see

entire document (e.g., the abstract; and page 974, Figure 1 and column 3). More particularly, King et al. discloses that a probe consisting of a 1 kbp restriction fragment of the cloned gene was used to detect and quantify a 6 kb Eco RI fragment of the gene; see, e.g., page 974, Figure 1. King et al. teaches that the results of the analysis indicated that the gene was amplified in nucleic acid derived from the MAC117 cells (page 974, column 3).

As apparent from the disclosure of King et al., the cloned gene that was amplified in the nucleic acid of MAC117 cells contains a nucleotide sequence encoding the amino acids encoded by the 423 nucleotides set forth in Figure 1 of this application; see page 975, Figure 2.

Although it does not appear that King et al. describes classifying the cancer cells, as explained in the above rejection of the claims as failing to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, it is not evident how the cancer must be classified, or what the active step of classifying the cancer actually entails, since it cannot be ascertained which attributes or features of the cancers to be classified are *correlated* with gene amplification or increased expression of the gene product. A "correlation" is a reciprocal relation between two or more things; and as such, it is not understood how the cancers must be classified because it is not apparent what relationship must be identified. For this reason, it cannot be known whether or when the objective of the claimed process is met, or whether or not any given process described by the prior art involves such an active step. Therefore, until shown otherwise, it is submitted reasonable to deem that the process disclosed by King et al. is materially and manipulatively indistinguishable from the claimed process.

Receipt of the declaration under 37 C.F.R. § 1.131 by C. Richter King, Matthias H. Kraus and Stuart A. Aaronson, which was filed on June 17, 1996, is acknowledged; however, this rejection is made under 35 U.S.C. § 102(b) and Applicant is reminded that a rejection under § 102(b) cannot be overcome by affidavits and declarations under § 1.131. See M.P.E.P. § 2133.02. Accordingly, any consideration of the merit of the declaration is present moot.

25. Claims 60, 61, 68, and 69 are rejected under 35 U.S.C. 102(b) as being anticipated by Coussens et al. (*Science*. 1985 Dec 6; **230**: 1132-1139).

Herein, claims 60, 61, and 68 are drawn to a process comprising detecting a MAC117 gene in a tissue or tumor cell by hybridizing nucleic acid derived from the tissue or tumor cell with a nucleic acid probe of the gene. This interpretation of the claims is considered reasonable since the claimed process is need not be practiced using tissues or tumor cells that necessarily contain amplified, rearranged, or overexpressed genes. Thus, the claims do not necessitate the detection of amplification, rearrangement or overexpression of a MAC117 gene; instead the claims simply require that a process comprise the step of hybridizing nucleic acid derived from the tissue or tumor cell with a nucleic acid probe of the gene. Claim 69 is drawn to a process of detecting a MAC117 gene by hybridizing nucleic acid with a nucleic acid probe of the gene.

Coussens et al. teaches a process comprising hybridizing nucleic acid derived from the tissue or tumor cell with a nucleic acid probe of the gene; see entire document (e.g., page 1134, Figure 2; and page 1137, Figure 5). More particularly, Coussens et al. teaches a Northern blot analysis of nucleic acid derived from normal and malignant tissues, which was performed using two different probes of the gene, which consisted of restriction fragments of cloned cDNA molecules that were derived from transcripts of the gene; see, e.g., page 1134, Figure 2. In addition, Coussens et al. teaches a Southern blot analysis of nucleic acid derived from human lymphoblastoid cells, mouse 3T3 cells, and various somatic cell hybrids of cells from humans and rodents using the same probes; see, e.g., page 1137, Figure 5.

As apparent from the disclosure of Coussens et al., the cloned gene that was amplified in the nucleic acid of various tissues or tumor cells contains a nucleotide sequence encoding the amino acids encoded by the 423 nucleotides set forth in Figure 1 of this application; see page 1135, Figure 3.

Although it does not appear that King et al. describes classifying the cancer cells, as explained in the above rejection of the claims as failing to satisfy the requirement set

forth under 35 U.S.C. § 112, second paragraph, it is not evident how the cancer must be classified, or what the active step of classifying the cancer actually entails, since it cannot be ascertained which attributes or features of the cancers to be classified are *correlated* with gene amplification or increased expression of the gene product. A "correlation" is a reciprocal relation between two or more things; and as such, it is not understood how the cancers must be classified because it is not apparent what relationship must be identified. For this reason, it cannot be known whether or when the objective of the claimed process is met, or whether or not any given process described by the prior art involves such an active step. Therefore, until shown otherwise, it is submitted reasonable to deem that the process disclosed by Coussens et al. is materially and manipulatively indistinguishable from the claimed process.

Receipt of the declaration under 37 C.F.R. § 1.131 by C. Richter King, Matthias H. Kraus and Stuart A. Aaronson, which was filed on June 17, 1996, is acknowledged; however, this rejection is made under 35 U.S.C. § 102(b) and Applicant is reminded that a rejection under § 102(b) cannot be overcome by affidavits and declarations under § 1.131. See M.P.E.P. § 2133.02. Accordingly, any consideration of the merit of the declaration is present moot.

26. Claims 60, 61, 68, and 69 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 4,968,603-A (of record; cited by Applicant).

Herein, claims 60, 61, and 68 are drawn to a process comprising determining whether a MAC117 gene is amplified or overexpressed in a tissue or tumor cell from a patient by hybridizing nucleic acid derived from the tissue or tumor cell with a nucleic acid probe of the gene, or alternatively by contacting cellular extracts of the tissue or tumor cell with an antibody that specifically binds to the protein encoded by the gene in an immunoassay; and claim 69 is drawn to a process of detecting a MAC117 gene by hybridizing nucleic acid with a nucleic acid probe of the gene.

U.S. Patent No. 4,968,603-A (Slamon et al.) teaches a process comprising determining whether a gene, which is designated "HER2/neu", is amplified in a tissue or tumor cell from a patient by hybridizing nucleic acid derived from the tissue or tumor cell

with a nucleic acid probe of the gene; see entire document (e.g., the abstract). Slamon et al. discloses that amplification of the gene is related to the status of neoplastic diseases, particularly breast adenocarcinomas; see, e.g., the abstract. Slamon et al. further discloses since gene expression corresponds to gene amplification that alternatively gene expression may be measured based on the level of mRNA transcription and/or gene product; see, e.g., column 3, lines 52-54. Slamon et al. teaches mRNA transcription can be measured by a variety of techniques, including Northern blotting, and that a variety of methods for measuring expression of the gene product exist, including Western blotting and immunohistochemical staining; see, e.g., column 3, line 52, through column 4, line 40.

Slamon et al. discloses that the gene that was amplified in the nucleic acid of breast tumor cells, for example, was independently isolated by other research groups and has been designated "MAC117" by one of these groups; as such, it would appear that the gene described by Slamon et al. is the same as the gene to which the claims are directed (i.e., a gene that contains a nucleotide sequence encoding the amino acids encoded by the 423 nucleotides set forth in Figure 1 of this application).

Receipt of the declaration under 37 C.F.R. § 1.131 by C. Richter King, Matthias H. Kraus and Stuart A. Aaronson, which was filed on June 17, 1996, is acknowledged; however, the declaration is ineffective to overcome this ground of rejection because: (a) it fails to establish that the acts were performed in this country; and (b) the scope of the declaration is not commensurate with the scope of the claims.

In particular regard to the latter reason the declaration is deemed insufficient, it is noted that the declaration provides, as evidence of an alleged reduction to practice of the claimed invention, a copy of the publication of King et al. However, while the claims are directed to a process for diagnosing any of a genus of human cancers, King et al. discloses only their detection of the amplification of a novel v-*erbB*-related gene in MAC117 breast cancer cells, pointedly indicating that "extensive studies will be required to determine the frequency of MAC117 gene amplification in different human malignancies" (page 975, column 1). Moreover, King et al. discloses that the gene was not amplified in A431 vulva epidermoid carcinoma cells (page 974, Figure 1) and that

"[a]nalysis of DNA from ten additional mammary carcinomas has not revealed amplification of the MAC117 gene" (page 975, column 1); so it seems that King et al. fails to establish that amplification of the gene in the MAC117 cell line was little more than anomaly. Furthermore, King et al. shows no evidence of either rearrangement of the gene or its overexpression in MAC117 breast cancer cells or any other cells. Such considerations support the position that the scope of the declaration is not commensurate with the scope of the claims.

Conclusion

27. No claim is allowed.

28. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Yamamoto et al. (*Nature*. 1986 Jan 16; **319**: 230-234) (of record) teaches amplification of a MAC117 gene in salivary adenocarcinoma and a gastric cancer cell line. Semba et al. (Proc. Natl. Acad. Sci. USA. 1985 Oct; 82: 6497-6501) teaches amplification of a MAC117 gene in salivary gland adenocarcinoma. Kraus et al. (*EMBO J.* 1987 Mar; **6** (3): 605-610) (of record; cited by Applicant) teaches amplification and/or overexpression of a MAC117 gene in human mammary tumor cell lines.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

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/Stephen L. Rawlings/

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slr
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